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Effects of Intravenous Dobutamine on Coronary Vasomotion in Humans

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OBJECTIVES We sought to investigate the vascular mechanisms of dobutamine-induced myocardial ischemia.

BACKGROUND Dobutamine stress is often used as a surrogate for exercise. The effects of dobutamine on the epicardial arteries are incompletely understood and possibly different from those of physical exercise.

METHODS Intravenous (IV) dobutamine (40 μg/kg per min) was administered in 19 patients with normal, 23 patients with mildly atherosclerotic, and 12 patients with stenotic coronary arteries. In another two groups of patients with stenotic arteries, IV dobutamine was preceded by 1) an intracoronary (IC) bolus of the alpha-adrenergic blocker phentolamine (12 μg/kg, n = 12); and 2) an IC infusion of the nitric oxide substrate L-arginine (150 μmol/l per min for 20 min, n = 11). Intravenous saline instead of dobutamine was infused into eight patients with normal arteries. After dobutamine (or saline), an IC bolus of isosorbide dinitrate (ISDN, 0.2 mg) was given. Coronary vasomotion was evaluated by quantitative coronary angiography on angiograms obtained after each dose of dobutamine, saline, phentolamine, L-arginine, and ISDN.

RESULTS Dobutamine increased the rate–pressure product and heart rate similarly in all patients except those who received saline. Dobutamine induced vasodilation in normal (change in luminal diameter [ΔLD] vs. baseline: 19 ± 2%) and in mildly atherosclerotic arteries (ΔLD: 8 ± 2%, $p < 0.05$ vs. normal). In stenotic arteries, dobutamine did not induce significant vasomotion (ΔLD: −3 ± 3%); the latter was improved by L-arginine (ΔLD: 10 ± 3%, $p < 0.05$ vs. stenotic arteries) and fully restored by phentolamine (ΔLD: 19 ± 3%, $p < 0.05$ vs. stenotic arteries).

CONCLUSIONS Endothelial dysfunction and enhanced alpha-adrenergic tone contribute to the loss of dobutamine-induced vasodilation in coronary atherosclerosis. In contrast to physical exercise, dobutamine does not induce "paradoxical vasoconstriction" of atherosclerotic coronary arteries. (J Am Coll Cardiol 2003;42:1596–601) © 2003 by the American College of Cardiology Foundation

Dobutamine stress echocardiography (DSE) is an accepted surrogate for exercise stress testing to detect significant coronary atherosclerotic disease (1,2). Several studies have shown that high-dose intravenous (IV) dobutamine can induce a mechanical dysfunction when an increase in oxygen

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demand induced by myocardial beta-adrenergic receptor stimulation is not matched by an adequate increase in coronary blood flow. In addition, IV dobutamine was shown to decrease the microvascular resistance to the same extent as intracoronary adenosine (3,4).

Nevertheless, DSE is clouded by a large number of false-negative results as compared with hemodynamic assessment of coronary stenosis (5). This may be partly due to the inability to detect regional wall motion abnormalities that occur in small territories. Alternatively, this might be due to a direct vasodilatory effect of dobutamine on atherosclerotic epicardial coronary arteries, an effect not observed during physical exercise. The latter induces "paradoxical" vasoconstriction of atherosclerotic arteries due to endothelial dysfunction and enhanced alpha-adrenergic receptor responsiveness (6–11). Dobutamine-induced vasomotion is thus the net result between dilatory forces (the endothelial component, through a flow-mediated metabolic response, and the direct stimulation of vascular and cardiac $beta_1$- and $beta_2$-adrenergic receptors [12–14]) and constrictive forces (the direct stimulation of $alpha_1$-adrenergic receptors of the vascular wall [13]).

Accordingly, in the present study, we investigated the vasomotion of epicardial arteries during dobutamine infusion in patients with normal, mildly atherosclerotic, and stenotic coronary arteries. In the latter setting, we further tested the hypothesis that paradoxical vasoconstriction to dobutamine does not occur.

METHODS

Patients and protocol. The study population consisted of 85 patients (24 women) with a normal left ventricular

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
DS = diameter stenosis
DSE = dobutamine stress echocardiography
IC = intracoronary
ISDN = isosorbide dinitrate
IV = intravenous
LD = luminal diameter
NO = nitric oxide
RD = reference diameter

ejection fraction referred for coronary angiography or percutaneous coronary intervention. In all patients, cardiac medications, except for aspirin and statins, were withheld for more than 36 h before the protocol, and no significant differences in the therapeutic regimen (e.g., angiotensin-converting enzyme [ACE] inhibitors, statins) were observed between groups of patients with stenotic coronary arteries (groups 4, 5, and 6). Patients with valvular heart disease, unstable angina, a recent myocardial infarction, conduction system disease, or clinical evidence of heart failure were excluded.

The patients were classified into six groups according to the angiographic data and pharmacologic protocol: group 1 consisted of 19 patients (83 coronary segments analyzed) with angiographically smooth coronary arteries (reference diameter [RD]: 2.2 ± 0.1 mm). In these patients, angiographic and hemodynamic data were recorded at baseline, during infusion of dobutamine (increasing dosages of 10, 20, 30, and 40 μg/kg per min for 3 min each step), as well as 1 min after IC isosorbide dinitrate (ISDN; 0.2 mg) given 10 min after cessation of the infusion of dobutamine, when the heart rate and blood pressure had returned to baseline. Group 2 consisted of eight patients (34 coronary segments analyzed) with smooth coronary arteries (RD: 2.2 ± 0.1 mm; p = NS vs. group 1). The protocol was identical to that of group 1, except that dobutamine was replaced by saline. This was done to rule out the potential influence of the contrast medium itself on epicardial vasomotion. Group 3 consisted of 23 patients (83 coronary segments analyzed) with diffuse, mildly atherosclerotic coronaries (<30% diameter stenosis; RD: 2.0 ± 0.1 mm). The pharmacologic protocol and regimen were identical to that of group 1. Group 4 consisted of 12 patients (36 coronary segments analyzed) with angiographically documented stenosis in at least one coronary artery (percent diameter stenosis [%DS]: 49 ± 4%). The coronary segments studied in this group all belonged to the stenotic artery. The pharmacologic protocol was identical to that of groups 1 and 3. Group 5 consisted of 12 patients (55 coronary segments analyzed) who fulfilled the same angiographic criteria as patients of group 4 (%DS: 47 ± 4; p = NS vs. group 4), but, 3 min before the start of dobutamine infusion, an IC bolus of phentolamine (12 μg/kg), a nonselective alpha-adrenergic blocking agent, was given (9). Group 6 consisted of 11 patients (63 coronary segments analyzed) with the same angiographic criteria as groups 4 and 5 (%DS: 47 ± 4; p = NS vs. groups 4 and 5), but, 8 min before IV dobutamine, an IC infusion (1.5 ml/min) of the nitric oxide (NO) precursor L-arginine (150 μmol/l per min for 20 min) (10,11) was started and maintained during dobutamine.

Catheterization protocol. A 6F sheath was introduced into the femoral artery, and a 6F guiding catheter was engaged into the coronary ostium. Heparin (5,000 U) was given to all patients, and in case of a coronary intervention, the dose was adjusted according to the body weight and need for glycoprotein IIb/IIIa receptor antagonists. On average, the duration of the protocol was 30 min, and the protocol was well tolerated by the patients. Informed consent was obtained from all patients before the diagnostic catheterization, in accordance with the protocol approved by the local ethical committee.

Data acquisition. Figure 1 summarizes the study protocols. An angiogram was acquired at baseline, 3 min after IC administration of phentolamine in group 5, 8 min after the start of IC infusion of L-arginine in group 6, during the last 15 s of each dosage of dobutamine (or saline) infusion, and 1 min after IC administration of ISDN. In each patient, an average of 4.1 segments were selected in one projection on the baseline angiogram. The coronary segments were considered as follows: in the left anterior descending coronary artery, the proximal (from the ostium to first septal branch), the mid (from the first to second septal branch), and the distal segment (after the second septal branch); in the left circumflex coronary artery, the proximal (from the ostium to first marginal branch), the mid (after the first marginal branch), and the proximal segment of the first marginal branch (the first 10 mm of the branch); and in the right coronary artery, the proximal (from the ostium to first acute marginal branch), the mid (from the first to second acute marginal branch), and the distal segment (after the second acute marginal branch). In dominant right coronary arteries, the proximal 10 mm of the right posterior descending artery was also considered. In groups 4, 5, and 6 (stenotic arteries), besides the stenosis, whenever possible, at least one segment proximal and one segment distal to the stenosis were obtained. In case of ostial stenosis, two or more segments distal to the stenosis were obtained. For each segment, the luminal diameter (LD) was measured at end diastole by quantitative coronary angiography using the catheter as a scaling device (3). In case of stenotic coronary arteries, changes in LD of the stenosis itself were first analyzed separately from the changes of the adjacent reference segments. For groups 4, 5, and 6, the data from the stenotic and adjacent reference segments were pooled, as a uniform response to dobutamine was observed.

To ensure proper filling of the coronaries with contrast medium, even during high-flow situations, an angioplasty guiding catheter was used in every case. Exactly the same projection was used at the different stages of the protocol. Based on the emergence of side branches, exactly the same

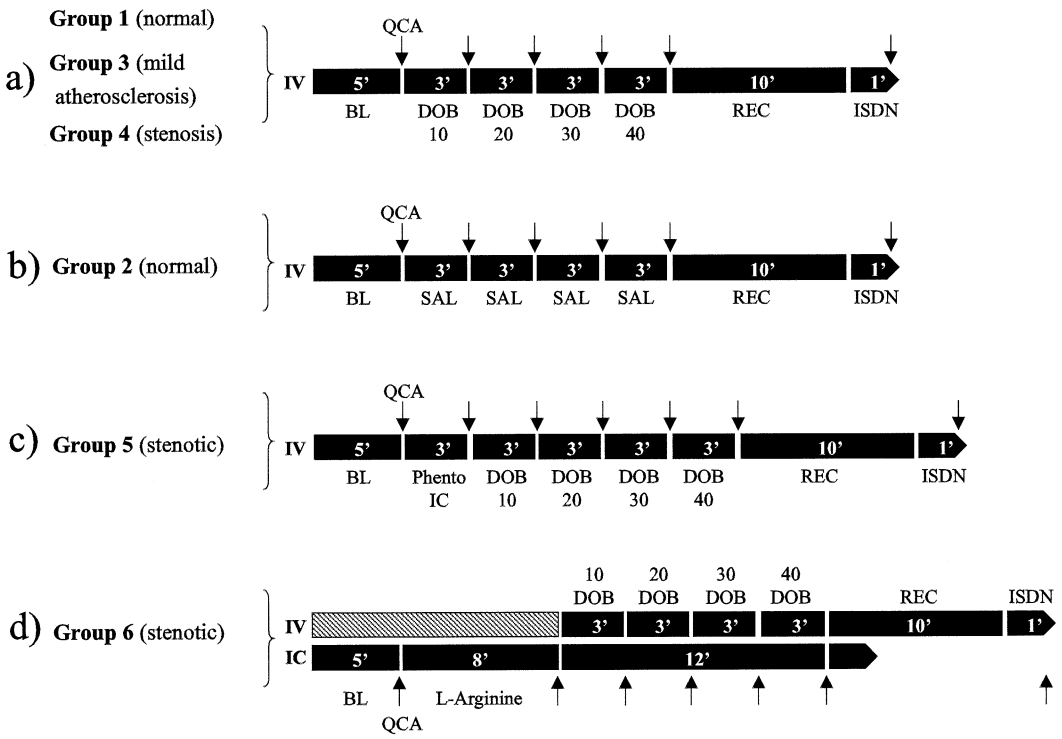

Figure 1. Study protocols. BL = baseline; DOB = dobutamine; IC = intracoronary; ISDN = isosorbide dinitrate; IV = intravenous; Phento = phentolamine; QCA = quantitative coronary angiography; REC = recovery period; SAL = saline.

segments were analyzed at the different stages of the protocol. Angiograms were recorded at 25 frames/s. Heart rate and blood pressures were digitally recorded (Notocord, France) during the entire study protocol.

The contrast medium used for all patients was the nonionic monomer, hypo-osmolar ioversol.

Statistical analysis. Data are expressed as the mean value ± SEM. Statistical comparison was made by analysis of variance (ANOVA) for repeated measurements to compare, within each group of patients, the effects of different doses of the drugs being tested. One-way ANOVA was used to compare the data between different groups. Post hoc analysis was performed with the Newman-Keuls test. Statistical analysis was performed with GraphPad Prism, version 2.0. P values >0.05 were considered nonsignificant.

RESULTS

Systemic hemodynamics (Fig. 2). Dobutamine induced a similar dose-dependent increase in the rate–pressure product in groups 1, 3, 4, 5, and 6. As expected, the administration of saline (instead of dobutamine) in group 2 patients did not produce any hemodynamic changes. The IC administration of ISDN after the end of the dobutamine/saline infusion was associated with a significant decrease of the rate–pressure product in all but group 2. In group 5, phentolamine administration produced a transient and nonsignificant reduction in blood pressure that was completely normalized after 3 min, when dobutamine infusion was started. No significant hemodynamic changes were observed during IC infusion of L-arginine.

Epicardial coronary vasomotion. The results of the drug regimen in the different groups are shown in Table 1 and Figures 3 and 4. In group 1 patients (normal coronary arteries), a significant dose-dependent increase in LD was observed during infusion of dobutamine. No further increase in LD was observed after ISDN. In group 2 patients (normal coronary arteries), saline infusion did not result in any change in LD, whereas ISDN significantly increased

Table 1. Changes in Luminal Diameter in the Different Groups of Patients

	Dob 10	Dob 20	Dob 30	Dob 40	ISDN
Group 1 (normal arteries)	3 ± 1*	8 ± 1*†	16 ± 2*†	19 ± 2*	22 ± 2*
Group 2 (normal arteries, but dobutamine replaced by saline)	0 ± 1	2 ± 1	−2 ± 1	2 ± 1	16 ± 2*†
Group 3 (mildly atherosclerotic arteries)	−1 ± 1	4 ± 2*	7 ± 2*	8 ± 2*	17 ± 2*†
Group 4 (stenotic arteries)	−6 ± 2*	−1 ± 2	−1 ± 3	−3 ± 3	18 ± 3*†
Group 5 (stenotic arteries pretreated with phentolamine)	2 ± 2	10 ± 2*†	15 ± 2*	19 ± 3*	20 ± 2*
Group 6 (stenotic arteries pretreated with L-arginine)	−1 ± 2	6 ± 2*	5 ± 3*	10 ± 3*	15 ± 3*†

*$p < 0.05$ vs. baseline (BL). †$p < 0.05$ vs. preceding value. Data are presented as the mean value ± SEM in percent changes compared with baseline.
DOB 10, 20, 30, and 40 = dobutamine at 10, 20, 30, and 40 μg/kg per min; ISDN = isosorbide dinitrate.

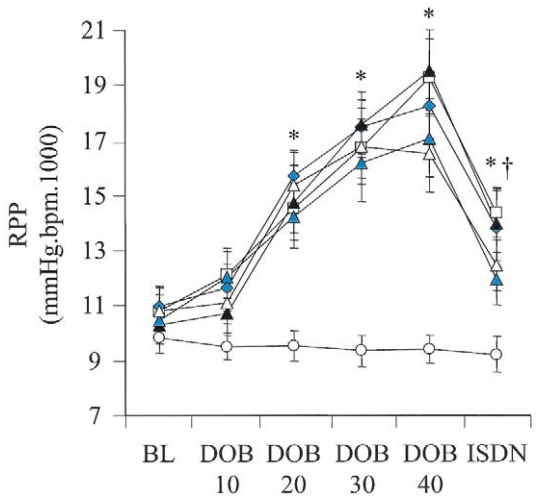

Figure 2. Effect of dobutamine (DOB) and saline on the rate–pressure product (RPP). *p < 0.05 vs. baseline (BL) for dobutamine 20, 30, and 40 μg/kg per min in groups 1, 3, 4, and 6; for dobutamine 30 and 40 μg/kg per min in group 5; and for ISDN in group 1. †p < 0.05 vs. preceding value in groups 1, 3, 4, 5, and 6. **White boxes** represent group 1 (normal coronary arteries); **white circles** = group 2 (normal coronary arteries, but dobutamine replaced by saline); **blue diamonds** = group 3 (mildly atherosclerotic coronary arteries); **black triangles** = group 4 (stenotic coronary arteries); **white triangles** = group 5 (stenotic coronary arteries, pretreated with phentolamine); **blue triangles** = group 6 (stenotic coronary arteries, pretreated with L-arginine).

LD. In group 3 patients (mildly irregular coronary arteries), a significant dose-dependent increase in LD was observed during infusion of dobutamine. Yet, this increase was significantly blunted as compared with group 1. Nevertheless, administration of ISDN resulted in a similar increase in LD as compared with the two previous groups. The data of groups 4, 5, and 6 take into account the stenosis and adjacent reference segments of the stenotic coronary artery.

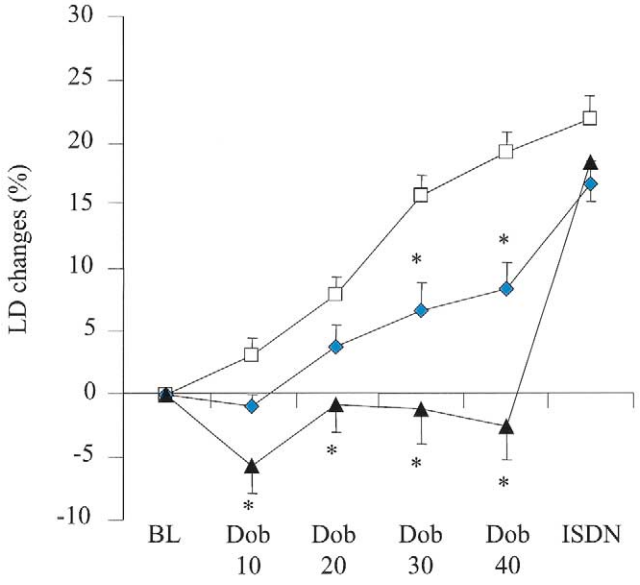

Figure 3. Effect of dobutamine on luminal diameter (LD) changes in group 1 (normal coronary arteries), group 3 (mildly atherosclerotic coronary arteries), and group 4 (stenotic coronary arteries). *p < 0.05 vs. group 1. For an explanation of symbols and abbreviations, see Figure 2.

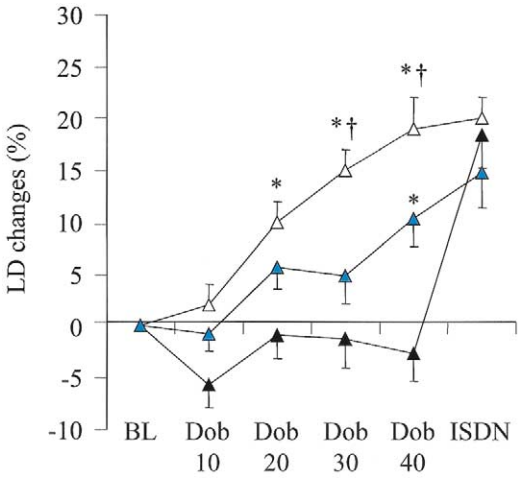

Figure 4. Effect of dobutamine on luminal diameter (LD) changes in group 4 (stenotic coronary arteries), group 5 (stenotic coronary arteries, pretreated with phentolamine), and group 6 (stenotic coronary arteries, pretreated with L-arginine). *p < 0.05 vs. group 4. †p < 0.05 vs. group 6. For an explanation of symbols and abbreviations, see Figure 2.

In group 4 patients (with angiographically significant stenosis), apart from transient, minor vasoconstriction occurring at 10 μg/kg per min, no significant vasomotion was observed. A significant increase in LD after ISDN could be detected. In group 5 patients (with angiographically significant stenosis), no changes in LD were observed after IC administration of phentolamine (change in LD of 1 ± 1% vs. baseline; p = NS). However, after alpha-blockade, the infusion of dobutamine induced dose-dependent vasodilation similar to that observed in normal arteries. Finally, in group 6 patients (with angiographically significant stenosis), no changes in LD were observed after 8 min of IC infusion of L-arginine (change in LD of −2 ± 2% vs. baseline; p = NS). Nevertheless, simultaneous administration of L-arginine and dobutamine was associated with improved vasodilation.

DISCUSSION

The present study demonstrates that atherosclerosis is associated with a progressive loss of dobutamine-induced coronary vasodilation. However, "paradoxical" vasoconstriction, as reported in patients with atherosclerosis during various forms of stress, was not observed with dobutamine. Dobutamine-induced vasodilation in patients with severe atherosclerosis is partially improved by pretreatment with L-arginine, an NO precursor, and fully restored by phentolamine, an alpha$_1$- and alpha$_2$-receptor blocker.

Effects of dobutamine in normal coronary arteries. Our data show that high-dose dobutamine induces a dose-dependent dilation of the normal coronary arteries, similar to intracoronary nitrates. The vasomotor response to dobutamine in group 1 is the consequence of direct and indirect mechanisms: dobutamine causes vasodilation by direct stimulation of alpha$_1$-, beta$_1$-, and beta$_2$-adrenergic receptors of the coronary vascular wall (12–14). Coronary beta-

adrenergic relaxation is partly mediated by NO release activation both in conductance (15) and resistive vessels (16). However, Ghaleh et al. (17) reported that the vascular smooth muscle cell component of beta-receptors is the main regulator of epicardial coronary vasomotion, and endothelium plays only an indirect role by enhancing the vasodilation via a flow-mediated mechanism. Of note, the distribution of beta-adrenergic receptors on coronary vascular wall is heterogeneous, as $beta_1$-adrenergic receptors are crucial in the regulation of coronary vasomotion in epicardial coronary arteries, whereas $beta_2$-adrenergic receptors become more important in the regulation of resistance coronaries (16,17).

In addition, dobutamine, by increasing contractility and myocardial oxygen consumption (18), leads to a release of vasodilatory substances such as adenosine, which acts on epicardial arteries and microvasculature (19). Finally, dobutamine, by increasing the heart rate, induces flow-mediated epicardial vasodilation (7).

Interestingly, other stress stimuli, including physical exercise, cold pressor testing, atrial pacing, and mental stress, induce vasodilation of normal coronaries, mainly via a flow-mediated mechanism (6–8).

Epicardial vasomotion in atherosclerosis. In contrast, in patients with atherosclerosis, the latter stimuli were shown to induce paradoxical vasoconstriction, presumably due to unopposed alpha-adrenergic vasoconstriction (20–23). The exercise-induced dilation of normal arteries is attenuated already at early stages of atherosclerosis in the presence of hypercholesterolemia (24) and hypertension (25) and with smoking (26). In the setting of angiographically documented coronary atherosclerosis, exercise is typically associated with vasoconstriction (8). Likewise, cold pressor testing and atrial pacing were characterized by a reversal of vasodilation to vasoconstriction with increasing severity of coronary atherosclerosis (6,7). Furthermore, mental stress and smoking have been demonstrated to have a similar vasoconstrictive response in atherosclerotic coronaries (22,27).

Our data suggest a progressive abolition of dobutamine-induced coronary vasodilation as a function of the severity of atherosclerosis. In contrast to what is observed during physical exercise, paradoxical vasoconstriction was not observed during high doses of dobutamine, not even in patients with angiographically significant stenoses. The small constriction at the lowest dose of dobutamine could be explained by a local vascular response through the alpha-adrenergic receptor stimulation, as supported by the fact that this constriction is turned into a dilation after alpha-blockade (group 5). It can be speculated that a dynamic equilibrium between vasoconstrictive forces (alpha-adrenergic receptors, endothelial dysfunction) and vasodilatory forces (beta-adrenergic receptors, both vascular and cardiac) is responsible for the absence of vasoconstriction during high-dose dobutamine. The significant additional vasodilation induced by IC nitrates (group 4, stenotic arteries) suggests that the absence of vasomotion during dobutamine is not due to vessel stiffness, and that the vascular smooth muscle cell component of the coronary wall is still working, allowing the diseased vessel to be responsive to constrictive or dilatory stimulation.

Role of the coronary endothelium. Progressive endothelial dysfunction could contribute to the loss of vasodilatory response to dobutamine. This can be related to the impairment of both the endothelial beta-adrenergic receptor component and the flow-mediated component of dobutamine-induced vasodilation. In fact, pretreatment with the NO precursor L-arginine of the stenotic coronary arteries improved coronary vasodilation to dobutamine, yet did not fully restore it.

Effects of alpha-receptor blockers. Several studies have suggested that paradoxical epicardial vasoconstriction in the presence of atherosclerosis is mediated by an unmasked alpha-adrenergic vasoconstriction (22,28,29). In patients with normal coronaries, no significant resting alpha-adrenergic tone has been found (13). Mildly atherosclerotic coronary arteries exhibit a more pronounced vasoconstriction to the selective $alpha_1$-agonist phenylephrine. The latter is paralleled by a vasoconstriction to acetylcholine, suggesting that endothelial dysfunction is responsible for the alpha-adrenergic hyper-responsiveness (23). Accordingly, vasoconstriction in response to the cold pressor test (28), exercise (29), or smoking (22) was abolished by nonselective alpha- or selective $alpha_1$-blockers in patients with coronary artery disease.

Our data demonstrate that the blunted vasodilatory response to dobutamine is also the consequence of enhanced alpha-adrenergic receptor tone. In patients with documented coronary stenosis, alpha-blockade, at dosages that evoke mainly a local effect (9), restored vasomotion in severely diseased coronary segments.

Clinical implications. Several studies have suggested that the sensitivity of exercise echocardiography was superior to that of DSE (30,31). This might be related to a higher level of oxygen consumption reached by physical exercise. In addition, as suggested by the present data, it might be related to the exercise-induced vasoconstriction that is not observed during dobutamine. Finally, the concomitant treatment with alpha-blockers of patients undergoing DSE could further contribute to false-negative results.

Study limitations. Some of the variables that might influence the inter- and intra-individual vascular response to dobutamine have not been addressed in the present study.

Concomitant medical therapy, even though mostly withdrawn 36 h before, might have influenced the vasomotor response to dobutamine. In particular, drugs like ACE inhibitors and statins, which improved the endothelial function, could enhance the vasodilation to dobutamine. However, in the groups of patients with stenotic coronary arteries (groups 4, 5, and 6), no significant differences were observed concerning concomitant drug categories.

Diurnal variations of the endothelial vasomotor response have been reported (32,33). In particular, coronary seg-

ments with dysfunctional endothelium showed a hyperresponsiveness in the early morning (32). Most of the patients recruited have been studied in the morning (between 8:00 and 11:00 AM). No difference was present between the several groups concerning the number of patients not studied during this time window.

Coronary angiograms have been obtained by contrast hand injection. This approach bears the following limitations: 1) the injected contrast volume is not constant; 2) the injection does not always start in the same part of the cardiac cycle; and 3) filling of the coronaries depends on the operator and vessel size. To minimize these sources of variability, 6F guiding catheters (instead of a diagnostic catheter) have been used in all patients, and long contrast injections (over three cardiac beats) have been performed.

Conclusions. Dobutamine induces a dose-dependent vasodilation in normal and mildly atherosclerotic coronaries, although a lack of vasomotion is observed in stenotic coronaries. The latter is related to the endothelial dysfunction and enhanced alpha-adrenergic responsiveness. The absence of paradoxical coronary vasoconstriction during dobutamine infusion may be partly responsible for the false-negative results of DSE.

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